

University of Dundee

Neurosurgical Treatments for Patients with Chronic, Treatment-Refractory Depression

Christmas, David; Matthews, Keith

Published in:
Stereotactic and Functional Neurosurgery

DOI:
[10.1159/000439115](https://doi.org/10.1159/000439115)

Publication date:
2016

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Christmas, D., & Matthews, K. (2016). Neurosurgical Treatments for Patients with Chronic, Treatment-Refractory Depression: A Retrospective, Consecutive, Case Series Comparison of Anterior Capsulotomy, Anterior Cingulotomy and Vagus Nerve Stimulation. *Stereotactic and Functional Neurosurgery*, 93(6), 387-392. <https://doi.org/10.1159/000439115>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Neurosurgical treatments for patients with chronic, treatment refractory depression: a retrospective, consecutive, case series comparison of Anterior Capsulotomy, Anterior Cingulotomy, and Vagus Nerve Stimulation

David Christmas *

Keith Matthews

Advanced Interventions Service, NHS Tayside & Division of Neuroscience, University of Dundee

* corresponding author. Area 7, Level 6, South Block, Ninewells Hospital and Medical School, Dundee, DD1 9SY. Tel: +44 (0)1382 496233. E-mail: david.christmas@nhs.net

Running head: A Comparison of Anterior Capsulotomy, Anterior Cingulotomy and Vagus Nerve Stimulation as treatments for Depression

Key Words: anterior capsulotomy, anterior cingulotomy, VNS, treatment refractory depression

This is the peer-reviewed but unedited manuscript version of the following article: ‘Neurosurgical treatments for patients with chronic, treatment refractory depression: a retrospective, consecutive, case series comparison of Anterior Capsulotomy, Anterior Cingulotomy, and Vagus Nerve Stimulation’, *Stereotactic and Functional Neurosurgery* 93:6 (2015): 387-392 (DOI: 10.1159/000439115). The final, published version is available at <http://www.karger.com/?doi=10.1159/0004391159>.

ABSTRACT

Background: The evidence base to guide therapeutic choices for patients with chronic and treatment refractory depression (TRD) remains weak. There is limited comparative information available to guide choice of intervention for patients with the most severe and disabling forms of illness.

Objectives: To describe the 12-month clinical outcomes for patients with chronic TRD treated with Anterior Capsulotomy [ACAPS] (n=5), Anterior Cingulotomy [ACING] (n=5), or Vagus Nerve Stimulation [VNS] (n=5).

Methods: A retrospective, consecutive, case series comparison.

Results: With clinical response defined as $\geq 50\%$ reduction from baseline MADRS score, response rates were: ACAPS (40%); ACING (60%); and VNS (20%). Adverse effects from all three procedures were relatively mild, consistent with previous reports and, in most cases, transient. Adverse effects from VNS were related to active stimulation, modifiable and diminished in severity over time. There were no deaths.

Conclusions: Although a small sample, our data represent a unique comparison of ACAPS, ACING and VNS for chronic TRD. The three cohorts were broadly equivalent in terms of baseline clinical characteristics, indices of chronicity, illness severity, and estimates of previous failed treatments. ACING and ACAPS, but not VNS, were associated with favourable response rates at 12 months.

INTRODUCTION

Comparisons between neurosurgical interventions for depression

There is no robust comparative literature for contemporary ablative surgery for the treatment of chronic, severe, treatment-refractory depression.

Kullberg [1] reported outcomes for a series of patients with different diagnoses treated by Anterior Capsulotomy (ACAPS) and Anterior Cingulotomy (ACING) (n=13 in each cohort) after at least 1 year follow-up. Using a categorical grading of function and perceived improvement, patients in the ACAPS cohort were considered to have experienced marginally superior outcomes, but at the expense of poorly specified and unmeasured “*personality changes*”. Unfortunately, the descriptions of the characteristics of these patients are difficult to reconcile with contemporary diagnostic concepts (“...*the target symptom was anxiety, on the basis of neurosis in 13, and early stage schizophrenia in one.*”) Importantly, there were no useful details with respect to chronicity, severity, or previous treatments, and lesion topography was unavailable.

Attempts to synthesise clinical outcomes in a manner that permits direct comparison [2-4] are fraught with bias, inaccuracy and uncertainty. For example: key clinical characteristics of patient populations are unreported or non-standardised; lesion characteristics rarely reported; and post-operative management plans rarely specified, let alone standardised.

Given the proliferation of neurosurgical interventions, primarily DBS-based, for psychiatric disorders since Nuttin and colleagues published their seminal report of apparent clinical effect of stimulation of the anterior limbs of the internal capsules in patients with OCD [5], there has been a compelling need to establish the relative efficacy of different treatments and targets to ensure that patients can provide informed consent to the procedure proposed. Establishing with confidence the comparative efficacy of different neurosurgical procedures for the management of TRD, as with any other clinical presentation, would require randomisation of patients meeting clearly defined study entry criteria, with a degree of standardisation of baseline illness and personal characteristics.

Unfortunately, there are no contemporary examples of such robust comparative studies. Indeed, three recent pivotal studies to test the efficacy of neurosurgical stimulation

treatments against even sham/placebo treatment have proven negative. For example, active VNS failed to differentiate from implantation plus sham stimulation in a large RCT [6] and there have been two large, multicentre, randomised, controlled trials evaluating the efficacy of DBS targeting either subgenual cingulate white matter tracts or ventral striatum/ventral capsule that were either negative [7] or discontinued in the light of futility analyses that suggested lack of efficacy [8].

Although *post hoc* sub-group analyses no doubt proceed apace to identify possible anatomical and stimulation parameter relationships that might reveal a covert therapeutic signal with both of these treatments, it is important to consider the possibility (or probability) that these therapies confer no benefit beyond those of non-specific / placebo effects.

Anterior Capsulotomy (ACAPS)

Thermal anterior capsulotomy was introduced by Lars Leksell in the 1950s for the treatment of and outcome in psychiatric illness (including 19 patients with depression) were reported by Torsten Herner in 1961 [9].

The lesions are placed in the anterior one third of the anterior limb of the internal capsule, and the target fibres connect the ventromedial orbitofrontal cortex and anterior cingulate cortex with the thalamus, amygdala, and hippocampus.

There are relatively few long-term follow-up studies reporting clinical outcomes for ACAPS for depression, but recent reports would suggest response rates of 50% [10]. Whilst ACAPS for anxiety disorders may be associated with an less favourable adverse effect profile [for example, 11], long-term follow-up of 20 patients with chronic, treatment-refractory depression failed to identify negative changes in personality or neurocognition [10].

Anterior Cingulotomy (ACING)

The anterior cingulotomy was introduced by Foltz and White in 1962, again for chronic pain [12]. The target site is similar to that of Anterior Cingulectomy, developed 10 years previously [13] and was popularised in the US by Ballantine for psychiatric illness and chronic pain [14]. The lesions of Cingulotomy target the cingulum bundle within the anterior cingulate gyrus, and also involve part of the anterior cingulate cortex.

Response rates to ACING for depression are typically in the region of 30% - 50% [15-17], although multiple factors may influence likelihood of response.

Vagus Nerve Stimulation (VNS)

VNS involves implantation of a pulse generator (similar in size to a cardiac pacemaker) in subcutaneous tissues in the left anterior chest wall. Electrodes are tunnelled under the skin and connect the pulse generator to the left vagus nerve in the neck. Typically for the treatment of depression, the pulse generator stimulates the nerve for 30 seconds every 5 minutes at a current of 1-2 milliamps.

Whilst a variety of reports of clinical outcome of VNS suggest response rates of 40%-50%, most patients in clinical studies did not have the kind of chronic, treatment-refractory depression typically seen in those undergoing ablative neurosurgery. However, in such patients response rates may still lie within the region of 30% [18]

METHODS

Objective

To describe the clinical outcomes at 12 months for consecutive patients with chronic, treatment-refractory depression (TRD) referred to the Dundee Neurosurgery for Mental Disorder / Advanced Interventions Service and ultimately treated between 1997 and 2004 with either Anterior Capsulotomy [ACAPS] (n=5), Anterior Cingulotomy [ACING] (n=5), or Vagus Nerve Stimulation [VNS] (n=5).

Treatment cohorts

Each treatment cohort represented the 5 most recent, consecutive, procedures for whom full 12-month follow-up data was available. Each patient reported here has been included previously within larger, single procedure case series [10; 17; 18]. The duration of follow-up reported here was limited to 12-months by some patients within each cohort (who were non-responders) going on to have further ablative procedures. Although there was overlap, the

patients were NOT operated on contemporaneously and treatment allocation was NOT randomised.

ACAPS patients were operated on in 1997 and 1998; ACING patients between 1999 and 2004; and VNS patients between 2001 and 2004. Prior to 1998, the '*procedure of choice*' in Dundee for patients with chronic TRD was ACAPS. In 1998, following reports of the relative efficacy and adverse effects of each procedure, a decision was made to switch to ACING as the '*procedure of choice*'. VNS became available as a treatment option from 2001 and was offered to patients as an alternative to ACING. The VNS cohort, therefore, *chose* this procedure over ACING. Also, therefore, the ACING cohort *chose* this procedure over VNS.

Inclusion criteria

All diagnoses were made by experienced clinicians and academic psychiatrists. Each patient met criteria for a primary diagnosis of either single episode, or recurrent Depressive Disorder according to ICD-10 and DSM-IV with minimum duration of index episode ≥ 24 months; although the actual duration was much longer. All patients were without significant psychiatric (Axis-I or Axis-II) or physical comorbidity. Diagnosis was determined in most cases by semi-structured clinical interviews (in the case of ACING and VNS patients) and was confirmed (in the case of the ACAPS patients) using OPCRIT [19].

Each patient had experienced very significant social and occupational impairment and had failed to sustain meaningful clinical response to a broad range of antidepressant medications and to sustained trials of psychological therapy with expert therapists.

Exclusion criteria

General exclusion criteria included: failure to satisfy the inclusion criteria regarding primary diagnosis; a current diagnosis of substance misuse fulfilling criteria for ICD-10 F10 to F19 mental and behavioral disorders due to psychoactive substance use; a diagnosis of organic brain syndrome fulfilling criteria for ICD-10 F00 to F09 including Alzheimer's disease, vascular and other dementias; a diagnosis of disorder of adult personality fulfilling criteria for ICD-10 F60 to F69; and a diagnosis of pervasive developmental disorder fulfilling criteria for ICD-10 F84. Other

specific exclusion criteria included previous ablative neurosurgery and previous vagotomy surgery (for the VNS cohort).

Ethical issues

Ten patients (66.7%) were not subject to any mental health legislation. Five patients (all ablative procedures; 33.3%) were subject to detention under either English or Scottish Mental Health legislation at time of surgery.

All patients were required to provide informed consent for surgery. In compliance with relevant Scottish Mental Health Legislation and best practice, all patients in receipt of ablative surgery were reviewed by Commissioners appointed by the Mental Welfare Commission for Scotland and independent clinical (and lay) opinion provided on adequacy of previous therapy; the suitability of the proposed treatment and capacity to provide informed consent to surgery.

Surgical Procedures

All surgical procedures were conducted under general anaesthesia. Volumetric CT and MRI images for ablative surgery were obtained parallel to the intercommissural plane for each patient and merged using the FrameLink Stereotactic Linking System (version 4. Medtronic Inc, Minneapolis, Minnesota, USA). For ACAPS surgery, details of surgical procedure are as for the larger case series reported by Christmas *et al* [10]. The bilateral target was 19-21 mm anterior to the anterior commissure. A 3 mm wide, 6 mm long radiofrequency probe was sited within the target such that its tip was at the inferior aspect of the target volume. Single lesions were made in each hemisphere by heating the probe to 70°C for 90 s using a radiofrequency lesion generator (Radionics, Burlington, Massachusetts). Additional bilateral lesions were similarly made such that the initial lesion was extended caudally to produce a total lesion within each capsule of approximately 18-20 mm in height and 8 mm in width.

For ACING surgery, details of surgical procedure were as for Steele *et al* [17]. A stereotactic frame ring was fixed parallel to the glabella-inion line and volumetric magnetisation prepared rapid gradient echo (MPRAGE) and coronal T2 magnetic resonance imaging (MRI) sequences, plus an axial computed tomography (CT) scan, 1 mm thick at zero angle, were obtained. Images were merged on a workstation using FrameLink software (version

4, Medtronic Inc, Minneapolis, Minnesota, USA). The bilateral targets were points 1 mm above the roof of the lateral ventricle, 7 mm lateral to the midline, and 20 mm posterior to the tip of the frontal horn. Radiofrequency lesions were made using a 6-mm exposed tip electrode and a radiofrequency lesion generator (Radionics, Burlington, Massachusetts). For each lesion, the tip was heated to 70°C for 90 seconds, repeated twice. The lesion volume contained both cingulum bundle and cortex.

For VNS surgery, details are as per Christmas *et al* [18]. VNS involved intermittent electrical stimulation of the left cervical vagus nerve using an implanted pulse generator in the left anterior chest wall using a commercial device, the NeuroCybernetic Prosthesis (NCP®) system (Cyberonics Inc., Webster, Texas, USA). Bipolar electrodes were wrapped around the left vagus nerve in the neck, near to the carotid artery, and connected to the stimulus generator. Thereafter, the treatment involved an intermittent stimulation of the afferent fibres within the left vagus nerve, with the intensity and frequency of generator firing controlled through the use of a telemetric wand connected to a personal computer. Stimulation parameters for the VNS-treated patients are shown in **online table 1**.

Clinical assessments

Objective assessments

Depressive symptoms were rated using the 17-item Hamilton Rating Scale for Depression [HRSD-17; 20] and the Montgomery-Åsberg Depression Rating Scale [MADRS; 21]. Global clinical outcomes were assessed using the Clinical Global Impression [22].

Self-report measures

The Beck Depression Inventory [BDI-II; 23] was used as the primary self-report depressive symptom measure for these cohorts.

Personality assessments

Personality was assessed in the majority of patients using the Personality Assessment Scale [24], completed with the patient and/or informant.

Categorical Outcomes

Standard criteria were used to define response and remission. ‘*Response*’ on the HRSD-17 was defined as $\geq 50\%$ improvement from baseline score with ‘*remission*’ defined as a score of ≤ 7 at 12 month follow-up. ‘*Response*’ on the MADRS was defined as $\geq 50\%$ improvement from baseline score with ‘*recovery*’ as a score of ≤ 10 at 12 months. ‘*Response*’ on the CGI-I was defined as achieving a score of 1 or 2 at 12-month follow-up.

Lesion topography

In order to calculate lesion locations, T2-weighted images were spatially normalised to the SPM T2 template (MNI space) and resliced to form 1mm isotropic voxels using SPM-2 [25]. For each scan, the centre of the lesion was estimated using regions of interest (ROI) created using MRIcro software [26]. Coordinates were reported in MNI space.

MRI scans were, unfortunately, unavailable for one ACAPS participants who was unwilling to attend Dundee for assessment. Clinical assessments were therefore completed at home.

Statistical analysis

Missing data were unavailable for a small number of cases. Baseline HRSD-17 scores and baseline BDI score were missing for one participant. These were imputed from MADRS score using regression models developed from contemporaneous HRSD-17, MADRS, and BDI-II scores in 256 patients (in the case of MADRS to HRSD-17) and 68 patients (in the case of MADRS to BDI-II). R-squared scores were 0.843 and 0.735 respectively, demonstrating the robustness of the model.¹

Twelve-month HRSD-17 scores were missing for two participants and 12-month BDI-II scores were missing for five patients. Again, these were imputed from MADRS scores.

Statistical analysis was performed using R software [27]. Normality of data was examined using the Shapiro-Wilk test and means \pm SD were reported for normally-distributed data, and medians (interquartile range) were reported for non-parametric data. Comparisons

¹ Available on request.

between groups were made using Chi-squared tests for categorical data, one-way ANOVA for normally-distributed continuous data, and Kruskal-Wallis test for non-parametric continuous data.

RESULTS

Patient characteristics

Detailed patient characteristics are summarised in **online table 2**.

The diagnostic breakdown of patients was as follows: F33.2 (Episode, severe without psychotic symptoms), N=2; F33.1 (Recurrent, moderate), N=4; F33.2 (Recurrent, severe without psychotic symptoms), N=8; F33.3 (Recurrent, severe with psychotic symptoms), N=1.

Categorical outcomes

Categorical outcomes are summarised in **online table 3** and show that ACAPS was associated with 2/5 (40%) patients achieving symptom improvement consistent with response and remission. This improvement was consistent using the HAMD₁₇, the MADRS and the CGI-I. ACING was associated with 3/5 (60%) patients achieving symptom improvement consistent with response. One (20%) of these patients also met criteria for remission. Again this was observed consistently using the HAMD₁₇, the MADRS and the CGI scales. VNS was associated with 1/5 (20%) patients meeting criteria for response on the MADRS and CGI, but not on the HAMD₁₇. There were no remitters in the VNS cohort at 12m.

This difference in the levels of improvement observed across the three cohorts was also confirmed by the magnitude of changes observed in estimated depression symptom burden (see **online table 4**). Absolute and percentage reductions in symptom burden in the ACAPS and ACING cohorts at 12-months were substantially larger than in the VNS patients (see **online table 5**).

Lesion topography

MNI coordinates of ACAPS and ACING lesions are shown below in **online table 6**. ACAPS and ACING lesion locations are shown on a spatially normalised brain in **online figures 1 and 2**.

Adverse effects

All adverse effects identified and reported immediately post-surgery and at 12-month follow-up period are summarised in **online table 7**. There were no deaths during the 12-month follow up (*still true at time of writing*). The only neurological event of note was a single post-operative seizure.

As might be predicted, ablative neurosurgery was associated with a greater burden of acute adverse effects in the form of headache and two of the ACAPS patients experienced some post-operative confusion. One ACING patient experienced a single post-operative seizure that did not require ongoing anticonvulsant therapy. At 12-month follow up, one patient described intermittent troublesome nausea and another an episode of urinary retention. (N.B. continuing intermittent urinary difficulties have required urological investigation). Subjectively, one ACAPS patient complained of concentration and memory difficulties although evidence of consistent neuropsychological change following ablative neurosurgery was not found and is summarised elsewhere [10; 17].

The burden of adverse effects experienced by the VNS patients was low and restricted to when stimulation was active. All patients managed to tolerate stimulation at a minimum output current of 1.25 mA and adverse effects diminished over time. Stimulation was associated with voice change and pharyngeal sensation / discomfort which was generally modifiable by reducing the stimulation pulse width.

DISCUSSION

We present unique data comparing the 12-month outcomes for three small cohorts of patients with TRD following non-randomised neurosurgical intervention with either ablative neurosurgery – ACAPS or ACING, or neurostimulation (VNS). The baseline characteristics of the patients within each cohort were consistent with the very chronic, highly disabling and markedly treatment refractory forms of illness that are features of the patients that are generally considered as potential candidates for neurosurgery within our clinical service.

There were no statistically significant differences between the cohorts at baseline and treatment adequacy was broadly comparable in all groups.

Response rates at 12-months were higher for those treated by ACAPS and ACING than with VNS. The mean magnitude of change in depression symptom burden was also greater in the ACAPS and ACING groups than in those treated with VNS. Although associated with a low adverse effect burden, VNS was not associated with a rate of response or degree of functional improvement comparable to that seen in patients treated by ablative neurosurgery (40-60%). Adverse effect burden within the ACAPS and ACING cohorts was higher than for VNS, but there were few persisting unwanted effects and there were no deaths. For patients with TRD of this chronicity and severity, and with this degree of functional impairment, ACAPS and ACING both appear to be relatively safe and effective interventions.

VNS is a safe, but relatively less effective intervention and may best be reserved for patients with less chronic and refractory forms of TRD. VNS patients here had a median of eight previous failed treatments in the current MDE and data from previous outcome studies have suggested that VNS response and remission rates decline with increasing levels of treatment non-response prior to VNS [28] although the rates of response to VNS in two larger series with comparable levels of prior non-response have been around 30-35% [18].

Limitations

This is a non-randomised comparison of three small cohorts and follow-up data only relate to the first 12-months following surgery. Assessors were not blinded to treatment condition. There was a small amount of missing data and adverse effect information was, historically, not collected systematically using specific tools designed to identify adverse effects (including at baseline). Open study designs such as this are unable to determine if clinical improvement reflects genuine response to the intervention or to reflect natural fluctuations in illness severity and / or response to non-specific effects (attention, structured care, placebo response etc.).

Conclusions

Despite the limitations within the evidence base, the conduct of ablative neurosurgery for psychiatric disorders continues. Based upon our small, single centre, non-randomised study of patients with chronic, disabling and highly refractory Major Depression, we propose that ACAPS and ACING appear more likely to be associated with beneficial clinical response than VNS.

Therapeutic trials of VNS may more appropriately be considered for patients at an earlier stage in the treatment pathway, prior to consideration for ablative surgery. Definitive, and necessary, trials comparing DBS / VNS and ablative neurosurgery for chronic and severe refractory Major Depression are awaited.

Acknowledgements

We wish to acknowledge the essential contributions made to this work by the following colleagues. The Dundee psychiatric neurosurgical programme was established by Professor George Fenton and Mr. T.K.Varma. Neurosurgical procedures prior to 1998 were performed by T.K Varma and subsequently by Muftah S Eljamel.

We are grateful to Professor Marwan Hariz for his comments on earlier drafts of the manuscript.

REFERENCES

- 1 Kullberg G: Differences in Effect of Capsulotomy and Cingulotomy; in Sweet WH, Obrador S, Martin-Rodriguez JG (eds): Neurosurgical Treatment in Psychiatry, Pain, and Epilepsy. Baltimore, University Park Press, 1977, pp 301-308
- 2 Freeman C, Crossley D, Eccleston D (2000) Neurosurgery for mental disorder. Report from the Neurosurgery Working Group of the Royal College of Psychiatrists. Council Report CR89. London: Royal College of Psychiatrists.
- 3 Andrade P, Noblesse LH, Temel Y, Ackermans L, Lim LW, Steinbusch HW, Visser-Vandewalle V: Neurostimulatory and ablative treatment options in major depressive disorder: a systematic review. *Acta Neurochir (Wien)* 2010;152:565-577.
- 4 Leiphart JW, Valone FH, 3rd: Stereotactic lesions for the treatment of psychiatric disorders. *J Neurosurg* 2010;113:1204-1211.
- 5 Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B: Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999;354:1526.
- 6 Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ: Vagus Nerve Stimulation for Treatment-Resistant Depression: A Randomized, Controlled Acute Phase Trial. *Biol Psychiatry* 2005;58:347-354.
- 7 Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone Jr DA: A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. *Biol Psychiatry* 2014;78:240-248.
- 8 Morishita T, Fayad S, Higuchi M-a, Nestor K, Foote K: Deep Brain Stimulation for Treatment-resistant Depression: Systematic Review of Clinical Outcomes. *Neurotherapeutics* 2014;11:475-484.
- 9 Herner T: Treatment of mental disorders with frontal stereotaxic thermo-lesions: A follow-up study of 116 cases. *Acta Psychiatr Scand* 1961;36 (Suppl 158):1-140.

- 10 Christmas D, Eljamel MS, Butler S, Hazari H, MacVicar R, Steele JD, Livingstone A, Matthews K: Long term outcome of thermal anterior capsulotomy for chronic, treatment refractory depression. *J Neurol Neurosurg Psychiatr* 2011;82:594-600.
- 11 Rück C, Andreewitch S, Flyckt K, Edman G, Nyman H, Meyerson BA, Lippitz BE, Hindmarsh T, Svanborg P, Mindus P, Asberg M: Capsulotomy for refractory anxiety disorders: long-term follow-up of 26 patients. *Am J Psychiatry* 2003;160:513-521.
- 12 Foltz EL, White LE: Pain "Relief" by Frontal Cingulumotomy. *J Neurosurg* 1962;19:89-94.
- 13 Whitty CWM, Duffield JE, Tow PM, Cairns H: Anterior cingulectomy in the treatment of mental disease. *Lancet* 1952;259:475-481.
- 14 Ballantine HT, Jr., Cassidy WL, Flanagan NB: Stereotaxic Anterior Cingulotomy for Neuropsychiatric Illness and Intractable Pain. *J Neurosurg* 1967;26:488-495.
- 15 Shields DC, Asaad W, Eskandar EN, Jain FA, Cosgrove GR, Flaherty AW, Cassem EH, Price BH, Rauch SL, Dougherty DD: Prospective Assessment of Stereotactic Ablative Surgery for Intractable Major Depression. *Biol Psychiatry* 2008;64:449-454.
- 16 Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, Price BH, Mayberg HS, Fischman AJ, Rauch SL: Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. *J Neurosurg* 2003;99:1010-1017.
- 17 Steele JD, Christmas D, Eljamel MS, Matthews K: Anterior Cingulotomy for Major Depression: Clinical Outcome and Relationship to Lesion Characteristics. *Biol Psychiatry* 2008;63:670-677.
- 18 Christmas D, Steele JD, Tolomeo S, Eljamel MS, Matthews K: Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients. *J Affect Disord* 2013;150:1221-1225.
- 19 McGuffin P, Farmer A, Harvey I: A Polydiagnostic Application of Operational Criteria in Studies of Psychotic Illness. Development and Reliability of the OPCRIT System. *Arch Gen Psychiatry* 1991;48:764-770.
- 20 Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatr* 1960;23:56-62.
- 21 Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatr* 1979;134:382-389.

- 22 National Institute of Mental Health: CGI: Clinical Global Impressions; in Guy W (eds): ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville, MD, National Institute of Mental Health, 1976, pp 218-222
- 23 Beck A, Steer R, Brown G: BDI-II, Beck depression inventory: manual; in (eds): Boston, Harcourt Brace, 1996
- 24 Tyrer P, Alexander MS, Cicchetti D, Cohen MS, Remington M: Reliability of a schedule for rating personality disorders. Br J Psychiat 1979;135:168-174.
- 25 SPM2 [Computer Program] (2003). Version for Microsoft Windows. London: Institute of Neurology, University College London. <http://www.fil.ion.ucl.ac.uk/spm/>.
- 26 MRlcro [Computer Program] (2005). Version 1.39 build 5 for Microsoft Windows. Nottingham: University of Nottingham. <http://people.cas.sc.edu/rorden/mricro.html>.
- 27 R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. <http://www.R-project.org/>.
- 28 Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK, Jr., Goodman RR: Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharm 2001;25:713-728.